REMARKS

Status of the Claims

Claims 22 and 29 are amended to specify the order of the two genes in the bicistronic construct with the gene encoding p14ARF being located in a first cistron downstream from the promoter and the gene encoding p53 being located in a second cistron downstream from p14ARF and wherein the second cistron is translated from an internal ribosoma entry site (IRES) located between the first and second cistron. Support for this amendment is found in the Example and in Figure 2.

Applicant reserves the right to pursue cancelled subject matter in divisional and continuation applications. Claims 40-41 finds support in the Example. Thus, the amended and new claims raise no issue of new matter.

Rejection of claims under 35 U.S.C. § 103(a)

Claims 22, 24-29, and 31-39 stand rejected under 35 U.S.C. 103(a) as allegedly being obvious over Roth et al. (US Patent 5,747,469) in view of any one of Lu et al. (Cancer Res. 62: 1305-1310, 2002), Tango et al. (Hum. Gene Ther. 13: 1373-1382, 2002), or DePinho (US Patent 6,613,750), Tiemann (WO 01/11063) and Dirks et al. (US Patent 6,060,273). Applicants respectfully traverse this rejection with respect to the amended claims, which now specify the order of the two genes in the bicistronic construct and the use of an IRES element between the two to initiate translation of p53 (i.e., p14ARF-IRES- p53).

An invention is unpatentable as obvious if the differences between the patented subject matter and the prior art would have been obvious at the time of invention to a person of ordinary skill in the art. Rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. KSR Int'l Co. v. Teleflex Inc., 127 S.Ct. 1727, 1741 (2007) (quoting In re Kahn, 441 F.3d 977, 988, 78 U.S.P.Q.2d 1329, 1336 (Fed. Cir.

2006)). Thus, in order to establish a *prima facie* case of obviousness, it is necessary for the Examiner to identify the reasons why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed. The proper analysis when determining obviousness includes consideration of the scope and content of the prior art; the level of ordinary skill in the prior art; the differences between the claimed invention and the prior art; and objective evidence of nonobviousness.

The primary rejection alleged by the Examiner is based on the combination of Roth et al. in view of any one of Lu et al, Tango et al., or DePinho et al., and in further view of Tiemann. The Examiner alleges that Roth et al. disclose a variety of viral vectors that express p53, for the treatment of various cancers. Office Action at p. 3, ¶ 3. The Examiner acknowledges that Roth et al. do not teach methods for killing p53-positive cancer cells and do not suggest the use of a bicistronic vector encoding p53 and p14ARF under the control of a single promoter. Office Action at p. 4, ¶ 1.

With respect to the combination of p53 with p14ARF for the treatment of p53-positive cancer cells, the Examiner turns to any one of Lu et al., Tango et al., and/or DePinho. The Examiner alleges that each of these references teaches that p53 and p14ARF, encoded on separate vectors, may be used in combination to kill p53-positive cancer cells. Office Action at p. 4, ¶ 2 through p. 5, ¶ 1. The Examiner acknowledges that none of these references teaches the use of a bicistronic vector encoding p53 and p14ARF under the control of a single promoter. Office Action at p. 5, ¶ 2.

With respect to the combination of p53 and p14ARF into a bicistronic vector and under the control of a single promoter, the Examiner turns to Tiemann and/or Dirks et al. Office Action at p. 5, ¶ 3 through p. 6, ¶ 1. The Examiner alleges that Tiemann discloses a vector that conforms with the requirements of the claims. The Examiner relies on Dirks et al. for general teachings regarding the construction of bicistronic vectors of the type encompassed by the rejected claims.

Applicants respectfully submit that the claims as amended are non-obvious over cited cited art because of missing claim elements and because the art does not motivate the combination of features as claimed. In the event that a prima facie rejection has been stated, Applicants submit that such has been rebutted by evidence of unexpected results, which results are provided in a new declaration by inventor Gjerset filed herewith.

A. The cited fails to teach or suggest all the claimed elements.

The claims as amended now require in the bicistronic construct a specific placement of the two genes, p14ARF and p53 relative to an IRES element. Thus, claims 22 and 29 require that the p14ARF be located in a first cistron downstream from the promoter and the gene encoding p53 be located in a second cistron downstream from p14ARF wherein the second cistron is translated from an internal ribosome entry site (IRES) located between the first and second cistrons.

The Examiner admits that Lu Tango and DePhino do not teach to use p14ARF and p53 in a bicistronic vector and looks to Tiemann or Dirks for such teaching. Dirks, however, only provides general teaching of bicistronic vectors and makes no mention of p14ARF or p53 and anything about the placement of such genes in a bicistronic relative to an IRES element. Tiemann contemplates bicistronics (Figure 1B) and contemplates inclusion of p14ARF and p53 in a bicistronic but provides not such vector and is silent as to the position of the two genes in such vector relative to an IRES.

Thus, the rejection fails because the cited art fails to teach or suggest all the elements of the claims.

B. The cited prior art provides no motivation to combine.

Applicants submit that a motivation to combine the art to teach the claimed invention is lacking. Rather than supporting the combination, Applicants respectfully submit that Dirks provides a teaching away. As described by inventor Gjerset in the attached Declaration, Dirks

teaches that in using bicistronic vectors with an IRES element, expression for the second and subsequent cistrons is always deficient compared to expression from the first "CAP-dependent" cistron. See Dirks, column 2-3. According to Dr. Gjerset, if one were motivated to make as bicistronic vector with p14ARF and p53, one would from the teaching of Dirks choose to put p53 in the CAP-dependent position directly following the promoter and p14ARF in the 2nd cistron following the IRES. This would be done, according to Dr. Gjerset, on the belief that one would get greater p53 expression than in the reverse and achieve better overall therapy than when p53 is placed in the second cistron position.

Thus, the rejection fails because Dirks teaches away from the claimed invention and, thus, would destroy motivation to combine upon which the present rejection is based.

C. Applicants demonstrate surprising and unexpected results using a bicistronic construct with p14ARF in the first cistron and p53 in the second cistron following an IRES element.

Even accepting, *arguendo*, that a *prima facie* case of obviousness has been made, it may be rebutted by evidence of an unexpected result. M.P.E.P. § 2144.08(II)(B) ("Rebuttal evidence may also include evidence that the claimed invention yields unexpectedly improved properties or properties not present in the prior art.").

In a new Declaration by Dr. Gjerset, submitted herewith, evidence is provided to show that the bicistronic Adp14/p53 vector with the gene encoding p14ARF in the first cistron position and the gene encoding p53 in the second cistron position with an IRES element between the two is an orientation that surprisingly results in enhanced translation of the p53 protein compared to the single gene p53 vector or compared to a combination of p14ARF and p53 single gene vectors. The evidence demonstrates a differential effect of p14ARF on CAP-independent translation versus CAP-dependent translation. This evidence means that the position of the p53 in following the IRES in p14/ARF/p53 bicistronic vector is critical to achieve maximal p14ARF and p53 levels in transfected cells. This evidence also explains why, as was shown in her previous declaration, that the bicistronic Adp14/p53 vector used (p14ARF-IRES-p53)

surprisingly results in 40 times the efficacy of the combination of p14ARF and p53 single gene vectors.

d. Claims 40-41 are non-obviousness over the cited art.

With respect to claims 40-41, which specifies killing of p53 positive cells is required, Applicants also submit that this claim is not obvious for the additional reason, as discussed in Applicants' Response of August 13, 2007, that Lu et al. and Tango et al. do not motivate the combination of p53 and p14ARF onto a single vector, under the control of a single promoter, for killing p53-positive tumor cells. The experiments described in both Lu et al. and Tango et al. use different amounts of the p53 and p14ARF vectors for infection. As such, they would not be amenable to combination into a single vector. Specifically, Lu et al. performs only a single experiment in which p53-positive cells are simultaneously infected with p53 and p14ARF. In this experiment, the A549 cells are infected with 100 pfu/cell of Ad-p53 and 40 pfu/cell Ad-ARF. See, Lu et al. at p. 1308, Figure 3. Likewise, Tango et al performs similar experiments using the p53-positive TE8 cells. In each of Tango's experiments, TE8 cells were infected with 5 moi Ad-p53 and either 10, 30, 50, or 100 moi of Ad-ARF. See, Tango et al. at p. 1376, Figure 2, and p. 1377, Figure 3B. The only instance in which Tango et al. used the same amount of p53 and p14ARF was in experiments using p53-negative cell lines (e.g., H358 cells; see Figure 5C).

A skilled artisan would not be motivated to construct a vector encoding both p53 and p14ARF under the control of a single vector for killing p53-positive cancer cells in view of the experiments described by Lu et al. and Tango et al. Both of these references detail experiments in which the levels of p53 and p14ARF are individually controlled; a feature lost by their combination under control of a single promoter. Furthermore, DePinho does not provide any additional relevant teaching as already argued.

In addition to the lack of motivation to combine, Applicants submit that the cited prior art fails to provide a reasonable expectation of success for killing p53-positive cancer cells using a bicistronic vector encoding both a p53 and p14ARF under the control of a single promoter. The

Examiner alleges that the skilled artisan would have reasonable expectation of success in light of the teachings of Roth et al. in view of any one of Lu et al., Tango et al., or DePinho, and Tiemann and Dirks et al. Office Action mailed 1/29/08 at p.7, ¶ 2. Applicants respectfully disagree and submit that the prior art provides no expectation of success in using the claimed bicistronic vectors for killing p53-positive cancer cells.

None of Roth et al., Lu et al., Tango et al., and DePinho teaches a bicistronic vector encoding p53 and p14ARF. At most, these references teach that the combination of p53 and p14ARF may be successful in killing p53 cancer cells when administered on separate vectors. The Examiner implies that the artisan has an expectation of successfully using p53 and p14ARF on a single vector and under the control of a single promoter based on the teachings of Tiemann and/or Dirks et al.

The teachings of Tiemann are irrelevant because Tiemann is only concerned with treating p53-negative cancer cells. Nothing in Tiemann indicates that the bicistronic vector could be successfully applied to p53-positive cancer cells. Any implication by the Examiner otherwise is mere speculation and hindsight reconstruction based on Applicants' disclosure.

Dirks et al. is also irrelevant to the expectation of success with regard to the use of p53/p14ARF bicistronic vectors for killing p53-positive cancer cells. Dirks et al. discloses the preparation of multicistronic vectors that result in the equimolar expression of the encoded polypeptides. Dirk provides limited examples of genes contained in the cistrons, but none of these genes include p53 or p14ARF. Dirks et al. at column 7, lines 2-9. Furthermore, nothing in Dirks et al. relates to killing p53-positive cancer cells. Thus, it will be erroneous to assume that the general teachings of Dirks et al. will be applicable to the specific case of a bicistronic construct of p53 and p14ARF under the control of a single promoter as asserted by the Examiner.

When taken together, the prior art relied upon by the Examiner fails to provide a motivation to use a bicistronic p53/p14ARF vector for killing p53-positive cancer cells and, based on the art, the artisan has no reasonable expectation of success. The art clearly

demonstrates a perceived need for independent regulation of the infective levels of each construct, thus negating the possibility of their combination into a single vector. Applicants respectfully submit that the Examiner has failed to make a *prima facie* case of obviousness. This rejection is traversed and should be withdrawn.

CONCLUSION

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741

Respectfully submitted,

Date 03/02/2009

By _____

FOLEY & LARDNER LLP
Customer Number: 30542
Telephone: (858) 847-6722
Facsimile: (858) 792-6773

Richard Warburg, Reg. No. 32,327
By Barry S. Wilson, Reg. No. 39,431
Attorney for Applicant